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REVIEW ARTICLE

DMEK graft: One size does not fit all

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Abstract

Descemet membrane endothelial keratoplasty (DMEK) is a popular procedure for the treatment of corneal endothelial diseases mainly targeting Fuchs endothelial corneal dystrophy (FECD) and pseudophakic bullous keratopathy (PBK). Although DMEK has multiple advantages, it is challenging in terms of graft preparation and delivery. One of the crucial factors of DMEK graft preparation is determining the size of the graft. Evaluating risks and benefits of transplanting larger or smaller grafts compared with the descemetorhexis performed following a standard DMEK procedure thus becomes important. Advanced techniques like pre-loaded DMEK requires pre-selection of graft diameter without physical examination of the eye making it more challenging. Therefore, recognizing the benefits of graft size and the number of transplanted endothelial cells becomes essential. Smaller DMEK grafts have been preferred and accepted for grafting. Larger diameter grafts have advantages but can be challenging due to higher detachment rates. We thus aim to review the challenges of preparing and delivering DMEK tissues with small or large diameter based on selected descemetorhexis area, discuss the outcomes based on different graft sizes, highlight related complications and suggest which cases may benefit from adopting smaller or larger graft size.

KEYWORDS

corneal transplant, descemetorhexis, DMEK, folding, graft size, large graft, small graft

1 | INTRODUCTION

The aim of surgical endothelial treatment is to replace the dysfunctional endothelial cells with healthy donor tissues. One of the crucial steps in endothelial keratoplasty (EK) is to identify correct descemetorhexis area and prepare the graft with an appropriate diameter, which can vary as the size of the affected area changes. Nowadays, the most common strategy involves EK in form of Descemet stripping automated endothelial keratoplasty (DSAEK) or Descemet membrane endothelial keratoplasty (DMEK). These tissues are often prepared as the same size that of the descemetorhexis (Stuart et al., 2018).

Smaller or larger graft size can be selected based on the given indication. It is well known that corneal endothelial cell density (ECD) is higher at the periphery compared with the central cornea, especially beyond 9.00 mm (Amann et al., 2003; Borroni et al., 2017; Parekh et al., 2019a,b; Romano et al., 2015; van den Bogerd et al., 2018). One of the major differences between the two most common surgical indications of EK (Fuchs' endothelial corneal dystrophy (FECD) and pseudophakic bullous keratopathy (PBK)) is the availability of healthy peripheral endothelium. In FECD, the peripheral endothelial cells tend to be normal, whereas dysfunctional endothelial cells have been found even at the periphery in PBK (Giasson et al., 2007).

As the corneal ECD is higher in the periphery, delivering larger or de-centred grafts could theoretically provide higher number of transplanted cells, which could potentially increase graft survival due to known strong relation between graft ECD and survival (Ishii et al., 2016; Romano et al., 2015). Although the use of a large DMEK graft is desirable, the size of the graft must be carefully customized, as it can lead to surgical complications. To obtain optimal results, the following factors must be considered: (1) donor preparation and (2) recipient characteristics. Here, we aimed to review the challenges of performing a correct descemetorhexis and preparing and delivering a DMEK graft with small or large diameter.

2 | CHALLENGES OF PERFORMING A DESCEMETORHEXIS

A key step in EK procedures is the removal of the recipient's diseased Descemet membrane (DM) and the associated endothelial cells (EC) (descemetorhexis) before transplanting the donor DM and EC. Sub-optimal visualization of the recipient DM during descemetorhexis can be responsible for inaccurate recipient DM removal. Balanced salt solution (BSS), ophthalmic viscosurgical devices (OVDs), trypan blue staining and air or their combination in the anterior chamber (AC) have all been proposed during this surgical step (Coco et al., 2021; Hamzaoglu et al., 2015; Jhanji et al., 2008; Terry et al., 2015). In DMEK surgery, similar to DSAEK surgery, a same size or slightly larger descemetorhexis compared with the implantable graft diameter is the most common strategy reported. A smaller than the graft diameter or incomplete descemetorhexis can leave tags of DM in the recipient eye, leading to increased risk of postoperative graft detachment. This further prevents optimal visual outcomes in cases where the diseased DM remnants remain in the graft–host stromal interface (Alió del Barrio et al., 2020; Chhadva et al., 2013; Kemer et al., 2021; Lavy et al., 2017; Vira et al., 2013). In parallel, a complete descemetorhexis has a consequence of annular postoperative oedema (outside of the graft) or intraoperative bleeding in case of contact with trabecular meshwork.

The risk of incomplete descemetorhexis has been well pointed out in case of DMEK after failed PK, with increased risk of graft detachment (Lavy et al., 2017). Subsequently, along with the standard stripping of the Descemet membrane (Schrittenlocher et al., 2020), other techniques, such as initiating descemetorhexis from the central area followed by enlarging it similar to performing a capsulorhexis using a Sinskey hook (DORC international BV, Holland) (Lavy et al., 2017), stripping the DM of the host within the edge of the PK wound, avoiding the graft–host junction (Pasari et al., 2019), using femtosecond laser to perform the descemetorhexis (F-DMEK) (Sorkin et al., 2019) and not performing the descemetorhexis at all (non-Descemet stripping DMEK, NS-DMEK) (Alió del Barrio et al., 2020), have been proposed. However, the lack of comparative studies limits identifying the optimum method for descemetorhexis.

However, in case of patients with previous glaucoma surgery, either with or without the glaucoma drainage device (GDD), no specific techniques or recommendations have been reported for descemetorhexis (Aravena et al., 2017; Birbal et al., 2019; Lin et al., 2019; Oganesyan et al., 2021; Schrittenlocher et al., 2021; Sorkin et al., 2020).

3 | CHALLENGES OF PREPARING A DMEK GRAFT ACCORDING TO THE GRAFT SIZE

Different graft sizes have been used, some of which routinely pursued, and the others often chosen based on the recipient requirement. These include large diameter (>9 mm), standard (8–8.5 mm), which may also occasionally include 7.5 mm and small diameter (<5 mm). Preparing a graft larger than 9 mm or smaller than 5 mm comes with its own challenges. The challenges of preparing a small DMEK graft include peeling, marking, loading and unfolding. Although graft scrolling has been reported to be multifactorial (Parekh et al., 2021), smaller graft size may or may not roll due to not having enough peripheral area to form a complete double roll and thus stay flat if stored in the media without any support.

In order to obtain a high-quality DMEK graft, its preparation step is crucial. Several techniques have been evaluated for preparing a DMEK graft (Birbal et al., 2018). Among these, the manual dissection was found to be associated with lowest endothelial cell loss (ECL) and tissue wastage and larger area covered by viable cells (Birbal et al., 2018; Parekh et al., 2018a,b) (Figure 1). Although studies of manual dissection showed graft sizes between

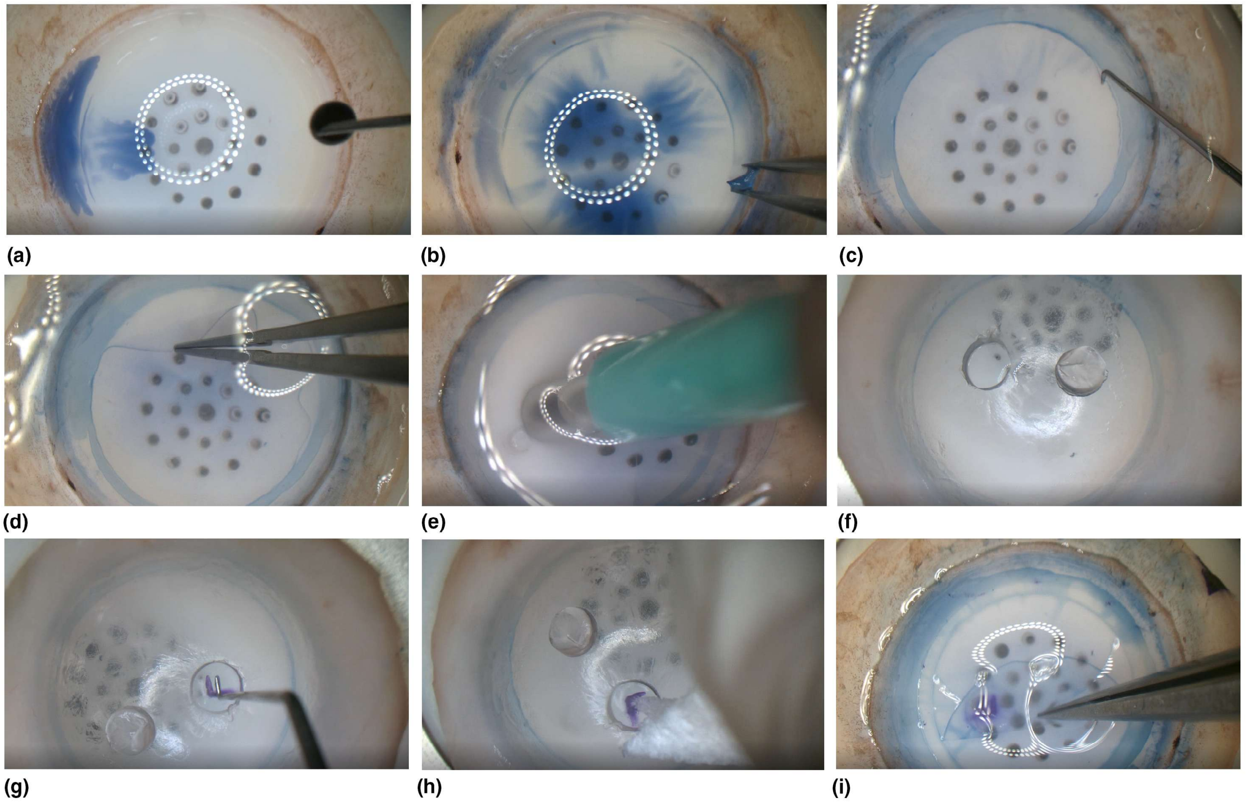

FIGURE 1 Standard manual peeling technique for DMEK. (a) the corneo-scleral rim is stained with trypan blue after centring the tissue on a trephine base, (b) a superficial cut is made using gentle tapping method with a desired diameter punch blade, stained to visualize the cut margin and the peripheral endothelium is removed using an acute forceps. (c) Cleavage plane is identified using a cleavage hook, and (d) the tissue is peeled from one end to the other leaving a hinge behind. (e) The stroma is punched using a 2 mm biopsy punch and the peeled DMEK is rested back on the stroma. (f) the punched stroma is removed after inverting the tissue with the epithelial cells facing the top and (g) the Descemet membrane is marked with the letter 'F' using a skin marker and the cleavage hook. (h) The stain is dried using a spearhead sponge and the stromal piece is placed back. (i) The tissue is inverted again with endothelial cells facing the top and folded manually for endo-in technique or placed in PBS to roll the tissue with endo-out for loading.

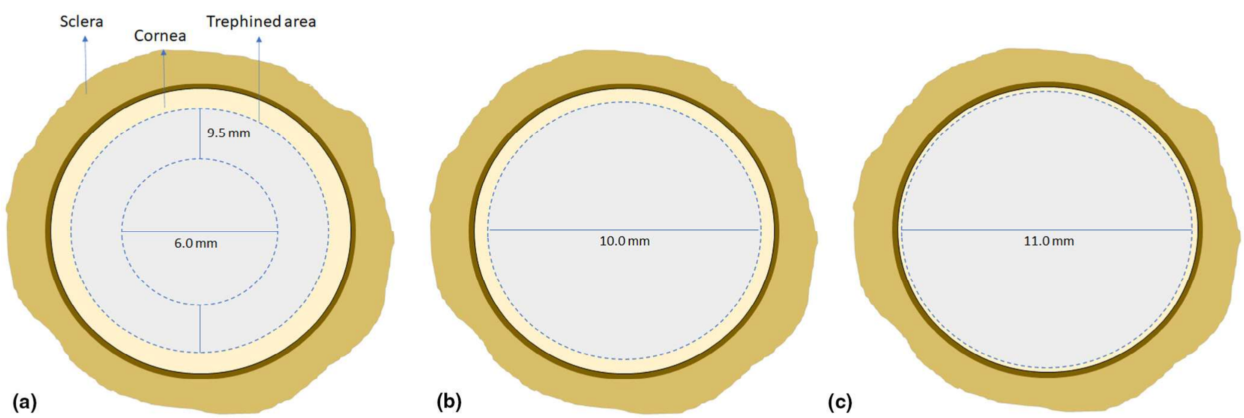

FIGURE 2 Common DMEK preparation procedures and their associated graft sizes. (a) Manual dissection with the use of a trephine or scoring that allows the preparation of a donor DMEK graft between 6.0 and 9.5 mm diameter size. (b) Hydroseparation or pneumatic dissection technique that separates the Descemet membrane from the stroma by injecting a liquid or an air bubble respectively has potential to obtain a 10.0 mm diameter graft. This procedure can be performed either by inserting the needle beneath the trabecular meshwork or peripheral scoring of the cornea followed by advancing the needle under the scored area. The bubble (air or liquid) is expanded until the DMEK graft is formed. (c) Hydrodissection technique is performed in two steps, which requires separating the Descemet membrane from the stroma using a liquid bubble formed by inserting the needle beneath the trabecular meshwork followed by manual trephination of the anterior lamella thus resulting into an 11.0 mm diameter graft.

6.00 and 9.5 mm (Figure 2a), those using hydroseparation (Parekh et al., 2014) or pneumatic dissection (Ruzza et al., 2015) report graft size over 9 mm (Figure 2b) with a single study on hydrodissection that reports graft size up to 11.0 mm (Figure 2c) (Salvalaio et al., 2014). However, despite the lack of studies reporting graft sizes larger than 9.5 mm in case of manual dissection, in theory, it is possible to obtain grafts with size of 10.0–11.0 mm, if the graft is scored at far periphery (Birbal et al., 2018).

Correct marking is essential as it can cause difficulties in identifying the correct orientation after delivering the graft in the anterior chamber. Marking with conventional skin markers (gentian violet) require approximately 2.00 mm diameter area and may lead to a higher percentage of cell death considering the area of the desired graft (Romano et al., 2018). However, other marking strategies proposed by Bala (2020), Tzamalis et al. (2020) or Muraine et al. (2013) suggest that trephines could be ideal to avoid additional cell loss. Preloaded DMEK with endo-in (DM-endothelium complex manually tri-folded like a 'taco' with endothelium facing inwards) (Figure 3a) can be challenging with small graft sizes (Busin et al., 2018; Parekh et al., 2017a,b; Parekh et al., 2022a,b). Small diameter graft does not have enough area to be manually folded and maintain the tissue architecture in the preservation/transplantation device hence, specialized devices need to be designed. On the other hand, pre-loading a DMEK tissue with endothelium outwards (Figure 3b) could be less challenging (Newman et al., 2018) with smaller graft sizes, considering that the graft in the device does not require maintaining a specific architecture but may or may not roll due to not having enough peripheral area to form a complete double roll (Figure 3c). A valid option for the eye bank would then be to ship a large diameter graft as pre-stripped (partially peeled with a small area attached to the periphery, such as a hinge), which can be trephined to a desired diameter by the surgeon. Other option for a small graft would be to strip and preserve the graft as a roll/flat tissue in the storage media. Such techniques have been shown on larger DMEK grafts (up to 9.00 mm diameter); however, it needs to be validated on smaller graft sizes (Parekh et al., 2017a,b; Romano et al., 2017).

The threats for a successful preparation of large diameter DMEK grafts are peripheral tears (Figure 4a), horseshoe-shaped tears (HSTs) (Figure 4b) and donor with previous cataract surgery (Figure 4c). Tissue selection therefore becomes important in such cases, mainly to avoid donors with central/peripheral scars or previous cataract surgeries (Parekh et al., 2017a,b). Any kind of tears can lead to unsuccessful donor DMEK preparation. Although peripheral tears as well as HSTs can be managed by excising a small piece of the periphery followed by separating the DM from the stroma and stripping it (Parekh et al., 2017a,b; Tenkman et al., 2014), they may lead to smaller diameter grafts with peripheral mortality. These factors can be easily managed if a smaller size graft is intended. It has been noted that donors with previous history of diabetes can be a risk factor for DMEK graft preparation (Greiner et al., 2014). Peeling such grafts can be challenging specifically at the central corneal region hence, preparing a small diameter decentralized graft would be ideal from donors with noted history of diabetes. Therefore, a small decentralized graft in such cases could be ideal to avoid the tissue wastage and also provide larger number of endothelial cells to be transplanted.

4 | IS THERE AN OPTIMAL SIZE FOR DMEK?

The choice of customized graft size can be based on several parameters, the easiest being the white-to-white (WTW) cornea diameter measurement. However, the WTW evaluation may not be enough exclusively, especially in complicated cases such as iris defects, the presence of glaucoma devices and/or previous keratoplasty surgeries (Alió del Barrio et al., 2020; Kemer et al., 2021; Lavy et al., 2017; Pasari et al., 2019; Quilendrino et al., 2017). Indeed, in these cases, AC area and posterior corneal profile must be considered while sizing a DMEK graft to reduce the difficulty of graft unfolding, facilitating its attachment and reducing the rate of graft detachment and ECL (Kemer et al., 2021; Maier et al., 2015; Pasari et al., 2019; Quilendrino et al., 2017). Therefore, it would be advisable to use a smaller graft in high hyperopic eyes and in patients with narrow anterior chamber.

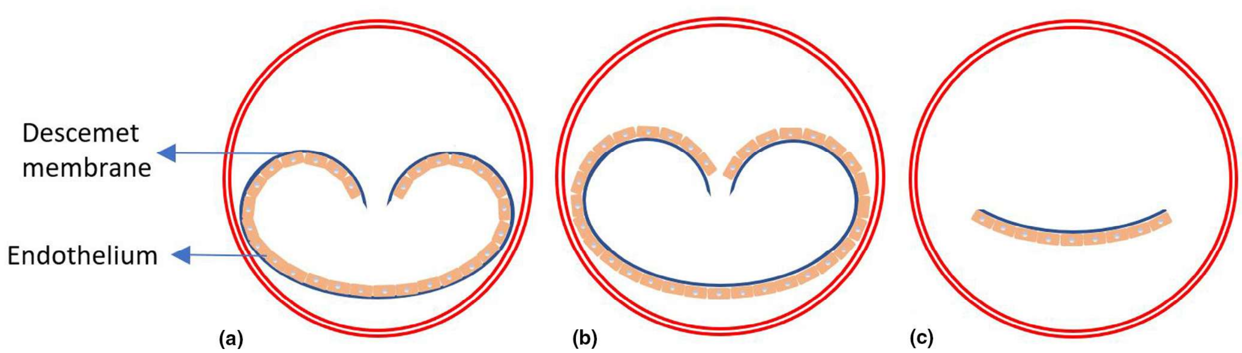

FIGURE 3 Endothelium inwards vs endothelium outwards. (a) Endothelium inwards technique refers to manual folding of the DMEK tissue with endothelium folded inside. (b) Endothelium outwards refers to natural rolling of the DMEK tissue with endothelium facing out. These techniques have been exploited specially while pre-loading the DMEK tissues. Standard diameter DMEK grafts (8–8.5 mm) have been used for both endo-in and endo-out with a few studies investigating endo-in technique with 9.5 mm graft. (c) A small diameter (≤5 mm) graft would be technically challenging while preloading a DMEK graft with endo-in method as the graft will lose its orientation; however, endo-out or a flat tissue can be delivered by injecting or using a bimanual pull-through technique if the tissue is marked or the orientation can be identified on a flat tissue with no graft scrolling.

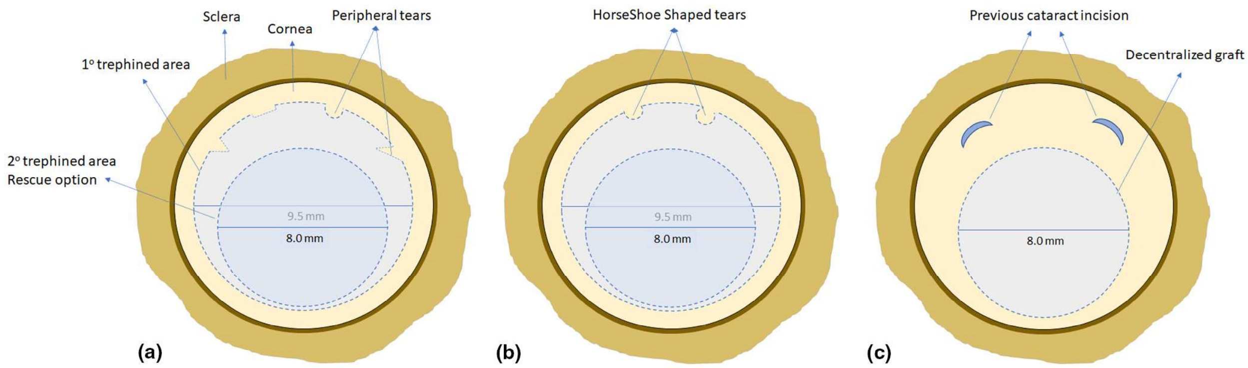

FIGURE 4 Common indications of graft preparation failure and their rescue options in the eye bank. (a) Following the primary (1°) trephination, fragile tissues can tear at the periphery while stripping. Multiple area can be selected to initiate stripping only on a large diameter graft. Once stripped, a decentralized smaller diameter (8.0 mm) graft can be prepared to avoid the peripheral tears. (b) Horseshoe-shaped tears can be rescued similarly. (c) Previous cataract incision at mid-periphery does not allow preparation of a successful large diameter graft hence, a decentralized relatively small diameter graft can be prepared to avoid tissue wastage. A decentralized graft also provides higher number of endothelial cells from the periphery.

Also, in case of eyes with previous GDD surgery, where DMEK has been reported as a feasible approach for the management of endothelial decompensation (Birbal et al., 2019; Lin et al., 2019; Oganesyan et al., 2021; Schrittenlocher et al., 2021; Sorkin et al., 2020), a smaller graft size may be beneficial, not only to better unfold and attach the graft, but also to avoid contact with the silicon tubes. Furthermore, 'three-quarter DMEK technique' has been proposed recently in patients with GDD, which requires performing two perpendicular cuts during graft preparation, and then remove one quadrant to better fit in the eyes with GDD (Oganesyan et al., 2021).

There is no clear evidence on a preferred graft size for DMEK after failed PK (Alió del Barrio et al., 2020; Kemer et al., 2021; Lavy et al., 2017; Pasari et al., 2019; Schrittenlocher et al., 2020; Schrittenlocher et al., 2021). Indeed, some authors suggest to slightly undersize the DMEK graft diameter (0.25–0.50 mm) compared with the diameter of the previously failed PK graft, in order to avoid the host–PK junction and lower the rebubbling rate (Alió del Barrio et al., 2020; Pasari et al., 2019). Other studies instead recommend not to oversize (Lavy et al., 2017) or do not show the differences in outcomes between oversized, same-sized or undersized (Schrittenlocher et al., 2020) .

Myopic and buphthalmic eyes, however, may benefit from grafts larger than 9.5 mm (Quilendrino et al., 2013a,b).

Larger graft size is recommended also in case of PBK in view of the presence of dysfunctional endothelium not only in the centre but also in the periphery (Giasson et al., 2007). Indeed, Zwingelberg et al. (2022)) reported 3-year outcome of DMEK for the treatment of FECD versus PBK. The results showed higher postoperative peripheral and central corneal thickness in case of PBK, with possible hyperopic shift for these patients in future. Subsequently, authors suggest that, even if ECL and BCVA was not different between the two groups at 3 years, patients could benefit from larger graft size in case of PBK (Zwingelberg et al., 2022), which was also supported by Inoda et al. (2020).

However, the rate of adoption of larger graft seems to be still low, as reported in a DMEK multicenter study where 93% of surgeons used DMEK grafts with diameters up to 8.5 mm, and only 7% used grafts larger than 8.5 mm (Dunker et al., 2021).

5 | DELIVERY AND UNFOLDING A DMEK GRAFT ACCORDING TO GRAFT SIZE

The correct delivery and implantation of donor graft in the anterior chamber of the host is important to reduce possible damage to the tissue (Dapena et al., 2009). Reported implantation technique of DMEK grafts according to the orientation of the endothelium include endothelium-inward (endo-in) or endothelium-outward (endo-out) (Parekh et al., 2017a,b; Parekh et al., 2022a,b; Price et al., 2018a,b). These two techniques do not differ in rate of ECL after implant, which, at 6 months, has been reported between 29.5% and 30.9% (Busin et al., 2018; Newman et al., 2018; Price et al., 2018a,b). Although endo-in may be advantageous in terms of achieving significantly lower unfolding time, endo-out takes much lesser time to prepare (Parekh et al., 2017a,b). Based on the selection, the next step is to choose the delivery technique. In case of 'endo-in', in order to preserve the architecture of the graft as 'taco fold', an injector is preferred (standard intra-ocular lens [IOL] cartridge), which may require an incision of 2.2–3.0 mm. This technique has shown a 6-month ECL of about 30% with the Viscojet 2.2 IOL Cartridge (Medicel AG, Wolfhalden, Switzerland) (Busin et al., 2016; Busin et al., 2018; Parekh et al., 2022a,b; Price et al., 2018a,b). Instead, in case of 'endo-out', the Straiko modified Jones tube has been used with reported ECL at 6 months of approximately 30% (Newman et al., 2018; Parekh et al., 2022a,b).

New devices for delivering the grafts using either technique with standard graft sizes and results have shown a lower ECL at 6 months. These new devices for preloaded DMEK may be helpful in case of smaller or larger graft, in order to reduce not only the tissue damage but also the preparation time. Recently, new storing and delivery device for endothelium-outward technique has been introduced by Geuder AG, named DMEK Rapid (Geuder AG, Heidelberg, Germany). The device has been found to be safe with ECL of 28.6% at 6 months (Rickmann et al., 2019; Wojcik et al., 2021). In case of endothelium-inward, the Coronet DMEK EndoGlide (Network Medical Products, North Yorkshire, UK) has shown a 6-month ECL of 26.6% (Ighani et al., 2021).

Most grafts are punched between 8 and 8.5 mm and the choice of unfolding technique is often based on the characteristics of the DMEK scroll in the anterior chamber as well as described by the algorithm published in 2013 by Liarakos et al. (2013) The standardized 'no touch' technique described by Dapena et al. (2011) is useful in cases with double Descemet rolls. The unfolding process is achieved using air on the top of the graft (in between the double roll or on the top of a partially unfolded graft) as an intraocular tool to manipulate the graft from the outer corneal surface. When most of the graft is unfolded, the air bubble can be enlarged to complete the unfolding, slightly pushing the graft onto the iris surface. Other techniques include the use of two cannulas to manipulate the graft from the outer corneal surface: the first one is used to press the host cornea against the iris to stabilize an unfolded flange of the DMEK graft, while the second one unfolds the other half with gentle tapping from the centre to the periphery (Liarakos et al., 2013). The single sliding cannula technique can be useful in cases of loose Descemet rolls, by simply applying gentle sliding pressure on the cornea with a cannula (Liarakos et al., 2013). Also, tapping on the outer corneal surface with two cannulas and simultaneous shallowing of the anterior chamber to facilitate graft–iris contact has been used to help the unfolding (Kocaba et al., 2018). Furthermore, the pull-through technique can assist graft delivery and positioning. A microforceps can be used to grasp the edge of an unfolded area of the graft, which is then pulled in the AC; gentle tapping on the outer corneal surface can help the unfolding of lateral folds (Busin et al., 2016).

Also, small peripheral venting incisions have been described to help the unfolding of peripheral graft edges. These incisions are similar to those described for DSEK surgery (Price & Price, 2006), that is higher in number (about 6) and smaller in size (around 1 mm). After air is introduced in the AC to secure the graft in place, small jets of water in the correct orientation through the peripheral venting incisions can be used to help unfolding the peripheral graft edges (Liu et al., 2017). Sarnicola irrigating cannulas have been designed to address challenges observed due to oversized grafts, although their use in the literature has been limited to grafts sized 7.75–8.00 mm for unfolding the peripheral edges (Sarnicola et al., 2019). There are no in vivo data regarding the pull-through technique in grafts sized 9–9.5 mm; however, an in vitro study on larger grafts (9.5 mm) showed that pull-through technique is a feasible option in such cases (Romano et al., 2017). The 'no touch' technique from Dapena et al. has also been described for larger grafts, sized 11–12 mm in buphthalmic eyes with good postoperative outcomes (Quilendrino et al., 2013a,b).

Delivering and unfolding grafts sized more than 8 mm are reportedly more difficult (Video S1 and S2) (Kruse et al., 2011; Lee et al., 2018). However, they have the advantage of being easier to centralize due to their relatively large diameter (Liarakos et al., 2013) and to transplant higher number of endothelial cells (He et al., 2012).

Different challenges are posed by graft of smaller sizes. Preclinical studies have shown specific challenges for 4 mm grafts, especially in cases with deep AC. The AC needs to be kept shallow during all surgical manoeuvres. Injection of both fluids and air in the AC was not found to be useful as the graft can move freely in the AC. The unfolding can therefore be achieved through gentle tapping and sliding of cannulas on the outer corneal surface (Dhubhghaill et al., 2021). In vivo studies on mini DMEK sized 3–5 mm in patients with corneal hydrops and consequently poor graft visualization proved that small grafts can be a feasible option. In these cases, graft unfolding was achieved by soft taps on the outer corneal surface while shallowing the depth of the anterior chamber (Bachmann et al., 2019). In contrast, studies on quarter DMEK from original graft size of 11.5 mm, which have an estimated size of a 6 mm graft, have shown that the unfolding can be achieved through indirect manipulation with the aid of air, fluids, taps and strokes on the outer corneal surface (Zygoura et al., 2018).

Unfolding time is the time required to unfold and attach the graft with air or gas tamponade. The endothelium-inward and outward DMEK graft study showed that the unfolding time of 9.5 mm diameter stripped graft was 4.92 minutes in the endothelium-outward group (Parekh et al., 2017a,b). Meanwhile, the study from Newman et al. (2018) showed that the unfolding time of 8 mm diameter endothelium-outward preloaded graft was 3.5 min. From these results, the unfolding time was shorter in smaller diameter graft, which could be anticipated by the smaller diameter graft having a smaller contact surface. Unfolding a graft can be influenced by the experience of a surgeon, the technique used, that is endo-in or endo-out, or the difference in surface contact according to the graft size. Indeed, smaller grafts have smaller contact surface facilitating faster unfolding compared with a large contact surface observed with larger grafts.

Attention must be particularly focused on cases with the presence of GDD, especially when considering the graft delivering and unfolding in eyes with previous glaucoma surgery. To reduce a higher rate of graft detachment and ECL in these eyes, the contact between the graft and the tube must be avoided, and the graft should be slowly unfolded over the tube, not over the iris and lifted against the recipient posterior stroma using an air bubble underneath (Birbal et al., 2019; Deshmukh et al., 2022). Furthermore, in case of air tamponade, repetitive air injections are advised to sufficiently pressurize the eye so that the anterior chamber can be filled at 100% with air for an average of >60 min, reducing the rate of graft detachment (Birbal et al., 2019). This procedure requires presence of peripheral iridectomy to prevent pupillary block. Moreover, glaucoma tubes may also be trimmed during the DMEK procedure.

6 | OUTCOMES ACCORDING TO DMEK GRAFT SIZE

6.1 | Graft detachment

Several risk factors have been reported in the literature for graft detachment, which includes learning curve (Birbal et al., 2020; Borroni et al., 2021; Vasiliauskaitė et al., 2020), history of glaucoma surgery (Aravena et al., 2017; Birbal et al., 2019; Lin et al., 2019; Schrittenlocher et al., 2021; Sorkin et al., 2020), failed PK (Alió del Barrio et al., 2020; Lavy et al., 2017; Pasari et al., 2019; Schrittenlocher et al., 2020), surgical complication during DMEK (Dunker et al., 2021) and recipient age (Dunker et al., 2021). PBK has shown a higher rate of graft detachment, compared with FECD in general, however, the results of 3-year follow-up showed no statistically significant differences (Zwingelberg et al., 2022).

Based on graft size, graft detachment has been found to be greater in the group of patients receiving larger grafts. Indeed Dunker et al. (2021) showed that out of 752 eyes; 144 (19%) had graft detachment that required rebubbling. Grafts with diameter of <8.5 mm showed 11.8% rebubbling, with 8.5 mm showed 13.2% rebubbling, and>8.5 mm showed 20.8% rebubbling. The univariable analysis showed an odd ratio of 1.19 and 2.13 for graft detachment requiring rebubbling in case of graft sizes 8.5 mm and>8.5 mm, compared with graft <8.5 mm. Recently, we showed a range of re-bubbling rate following preloaded DMEK transplant (26%–56%). It was noted that larger graft size in combination with longer preservation time can increase the risk of rebubbling (Parekh et al., 2022a,b).

Higher risk of graft detachment in case of larger graft may be explained by the contact area of the gas or air bubble with the graft. We speculate that larger graft would require a higher anterior chamber filling of air/gas, which may lead to higher risk of pupillary block.

6.2 | Endothelial cell density and cell loss, and graft survival: Short-term versus long-term outcomes

Evaluating the short versus mid/long-term outcome of ECL following graft sizes </> 8 mm seems to have no substantial differences. However, the literature is limited, as most studies refer to standard graft size (8–9 mm), with generally low number of patients with bullous keratopathy (BK) and, lack of use or comparison among different graft sizes. Furthermore, the possible presence of confounding risk factors would require the univariable analysis in each study to better estimate the impact of graft size on ECL and graft survival rate. These limitations prevent clear assessment whether larger graft with more endothelial cells would have longer graft survival. It is therefore important to report the findings and to have a reference value for evaluating the relationship between ECL, graft survival and graft size.

Earlier studies reported 30.8% ECL with 9 mm diameter grafts (Ham et al., 2009), while 8.5–9 mm diameter grafts presented an ECL of 32% (Price et al., 2009). Since then, the rate of ECL around 30% at 6 months has been almost always constant in case of a standard DMEK surgery where new surgical techniques, devices or learning curves are not involved (Ang et al., 2016) .

Chamberlain et al, with 8 mm diameter grafts, reported an ECL of 29.16% at 6 months and 33.06% at 12 months (Chamberlain et al., 2019). Busin et al. using 8.25 mm grafts showed an ECL of 29.5% (Busin et al., 2018). Arslan et al. showed an ECL of 28.3% and 29.7% in a comparative study between 8 mm and 9.5 mm grafts, respectively (Arslan et al., 2019).

Long-term results, up to 10 years have been reported with 9 mm (Birbal et al., 2020; Ham et al., 2016; Vasiliauskaitė et al., 2020) and 8 mm grafts (Schlögl et al., 2016; Weller et al., 2022).

At 5 years, the ECL with 9 mm graft was between 55 and 59% with a graft survival of 83–90%. At 10-year, the ECL and cumulative graft survival were 68% and 79%, respectively.(Vasiliauskaitė et al., 2020). Number of eyes with BK were 32/500 (6.4%) (Birbal et al., 2020) and 2/100 (2%) (Vasiliauskaitė et al., 2020). Weller et al. (2022) at five years, reported an ECL of 44% and cumulative 5-year graft survival of 95% (Schlögl et al., 2016) following an 8 mm diameter graft. At 10 years, the ECL was 72%, but cumulative survival rate was not assessed. The cohort of patients who finished the 10-year follow-up did not include any case of PBK (Weller et al., 2022) while only 1 patient was included with PBK at 5-year follow-up.(Schlögl et al., 2016).

Another study by Price et al. focused on the long-term outcome of 8.5–9 mm diameter graft and reported an ECL of 48% and cumulative 5-year graft survival of 93%, in case of 705 eyes with FECD (Parekh et al., 2018a,b). Thus, two factors, (a) the lack of a consistent number of studies comparing the ECD, ECL and graft survival according to different DMEK graft sizes with underlying pathology (FECD, PBK, failed PK or endothelial decompensation in patients with GDD); and (b) long-term studies with more than 10 years of follow-up would be essential to conclude the effect of different graft sizes on ECL and long-term survival.

From these studies, summarized in Table 1, although ECL was found to be slightly greater in almost all the cases with larger grafts, its true clinical relevance needs further investigation. Indeed, it appears that the ECD of DMEK grafts could drop below 500 cells/mm^2 in 12–15 years after the transplant given the rate of ECL reported in the studies. Over time, larger graft size may have a higher survival rate given the higher number of transplanted endothelial cells (Amann et al., 2003).

One of the factors can be the limitation of the instruments used for ECD count. Indeed, Quilendrino et al. routinely used 9.5 mm DMEK grafts and provided an interesting hypothesis on why an ECD decline was seen for large grafts (Quilendrino et al., 2013a,b). Postoperative corneal detergescence after DMEK affects almost exclusively the posterior surface, leading to an increase in its arc length so that the endothelial cells must 'stretch' and cannot be accurately measured with the fixed frame of the specular microscope.

7 | CONCLUSION

Graft detachment, re-bubbling, postoperative ECL, complications and rejections can be multifactorial

TABLE 1 Comparison of graft size with various parameters

Study	Follow-up	Graft size (mm)	N° eyes at baseline	N° bullous keratopathy	Mean reduction of endothelial cell density at end of follow-up
Ham et al. (2009)	6 months	9	50	0	30.8%
Price et al. (2009)	6 months	8.5–9	60	1 (1.7%)	32%
Busin et al. (2018)	6 months	8.25	46	0	29.5%
Chamberlain et al. (2019)	6 months	8	25	1 (4%)	29.16%
Arslan et al. (2019)	6 months	8 and 9.5	100	48 (48%)	28.3% (8 mm graft) – 29.7% (9.5 mm graft)
Schlögl et al. (2016)	5 years	8	97	1 (1%)	44%
Price et al. (2018a, b)	5 years	8.5–9	705	0	48%
Birbal et al. (2020)	5 years	9	500	32 (6.4%)	55%
Vasiliauskaitė et al. (2020)	10 years	9	100	2 (2%)	68%
Weller et al. (2022)	10 years	8	66	0	72%

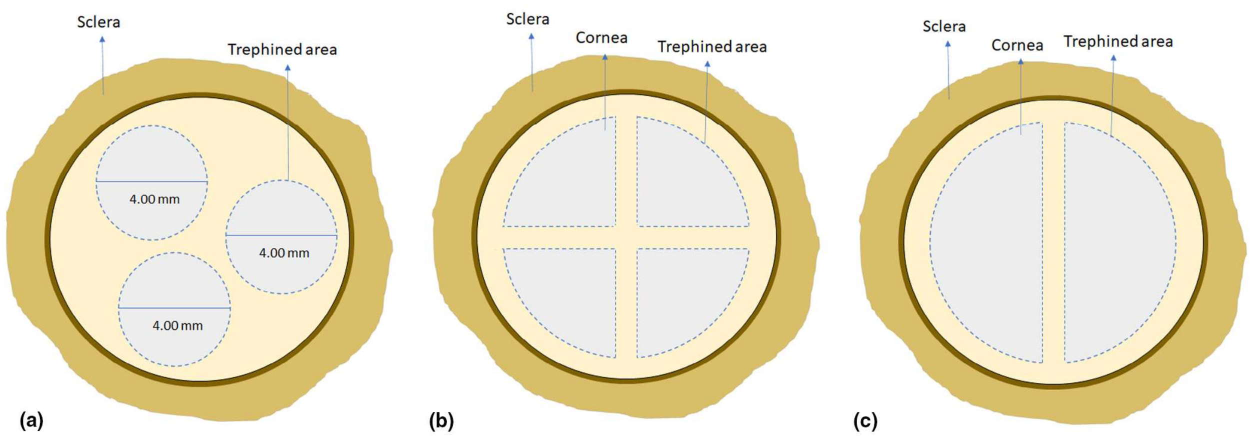

FIGURE 5 Increasing the number of transplants from a single donor. (a) Three 4 mm diameter grafts can be obtained from a single cornea, (b) quarter-DMEK has been proposed to prepare four small diameter DMEK grafts from a single donor cornea or (c) hemi-DMEKs, that is two grafts can be prepared by splitting one round graft into two forming 'half-moons'. All the techniques have a possibility to obtain certain number of peripheral endothelial cells, which could be promising for long term graft survival.

(Parekh et al., 2018a,b) and centre-centric (Parekh et al., 2022a,b). However, graft size to descemetorhexis is one of the crucial parameters to be considered before performing EK. Several studies have reported confounding factors. However, it appears that there is a general consensus on the use of a standard graft diameter. Selecting the graft diameter relies on two main aspects, the recipient requirement and long-term graft survival. With the advent of pre-loaded DMEK grafts, the selection of graft diameter becomes even more challenging as it must be pre-customized and cannot be performed on the table following physical eye examination of the patient. Therefore, knowing the advantages of graft size and the number of endothelial cells being transplanted becomes essential for such cases.

The benefits of having a small graft are manifold, such as it becomes easier to obtain multiple grafts from a single donor tissue depending on the incision sites. In fact, Dhubhghaill et al. (2021) tested the feasibility of obtaining 3 grafts of 4 mm diameter from a single donor cornea (Figure 5a), or using non-round shape graft, as 'quarter' (Figure 5b) and 'hemi' DMEK (Figure 5c) (Lam et al., 2014; Zygoura et al., 2018) showing the possibility and expanding the number of transplants further helping in reducing the donor corneal shortage (Gain et al., 2016; Romano et al., 2019); however, which comes with certain degree of challenges. As the scars due to previous cataract incisions are present in the mid-periphery, usually due to two incisions, it leaves enough area to prepare a relatively smaller size DMEK graft with a possibility to avoid peripheral tears and punch the tissue mid-centrally to obtain a clear graft with no HSTs. Decentralizing DMEK grafts with smaller sizes may reduce the risk of tissue wastage and add rejected corneas due to contraindications into the transplantable list. This would further increase the ECD, viable and putative stem cells as it involves the periphery of the graft. Considering that the peripheral cells are healthier, it may further increase long-term graft survival compared with the routine small DMEK grafts. Graft attachment is better and quicker with slightly low re-bubbling rate in such cases. If the tissue is torn in the optic zone, that is central 5–5.5 mm diameter (central tears), obtaining a standard central DMEK graft of 8.25–8.5 mm diameter is not possible and the tissue is usually discarded, which can be easily managed with smaller grafts by obtaining the tissue from the periphery that helps in reducing the discard rate of the precious human tissue (Anshu et al., 2013;

Quilendrino et al., 2013a,b; Terry et al., 2011). Hence, we recommend young surgeons with limited experience to start with grafts sized 7.5 mm, but progress to larger or smaller grafts according to the patients' needs.

There are limitations of using a small graft, such as peeling a small DMEK grafts and maintaining EC viability in the given area; marking, preserving and loading the graft, which has not been fully standardized yet; transplanting, opening and adjusting the graft in the given descemetorhexis area; ECL and long-term graft survival and; handling these grafts with conventional surgical devices and instruments may lead to higher percentage of ECL considering that the number of cells transplanted are relatively less than the traditional large size DMEKs. Although pre-loaded DMEK with endothelium outwards seems like a viable option with small sized grafts, it is equally challenging in terms of preparing the pre-loaded DMEK grafts with endothelium inwards. However, new devices such as DMEK Rapid and Coronet DMEK EndoGlide may be adopted for smaller grafts (Ighani et al., 2021; Parekh et al., 2022a,b; Wojcik et al., 2021).

On the other hand, a larger DMEK graft has multiple advantages, such as more EC for transplantation including peripheral cells; ease of preparing, marking and loading the graft; possibility of preparing a pre-loaded DMEK with endothelium inwards and outwards; ease of handling the graft while transplanting and better chances of long-term graft survival. However, larger diameter grafts can be challenging during attachment and can lead to higher detachment rates.

Therefore, it appears that the grafts can be customized depending on the recipient requirement for example a young recipient can receive a larger diameter graft for possibly long-term graft survivability, and myopic and buphthalmic eyes can benefit from larger than 9.5 mm grafts. Furthermore, comparative studies between DMEK in FECD versus PBK with different graft sizes will be necessary to better assess the outcome of larger grafts in case of PBK.

A patient with hyperopic eye or with small central guttae area can have a smaller graft to retain its healthy peripheral endothelial cells. This would further aid in reducing the shortage of donor availability by obtaining more grafts from a single donor.

In conclusion, most papers focus on graft preparations, delivery and unfolding techniques with main outcomes in terms of ECL, graft detachment and survival rate. However, lack of prospective comparative studies using different graft sizes, in view of 'one size does not fit all' would be necessary for further standardizing DMEK.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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